

EFFICACY REVIEW
by Mark Suarez, Entomologist - IB

Mark E. S.
18 January 2006

DATE: 18 January 2006

EPA REG. NUMBER: 73510-2
73510-5

PRODUCT NAME: Marketquest One Drop Flea & Tick Control
[73510-2]
Marketquest One Drop Flea & Tick Control
with IGR [73510-5]

REGISTRANT: Marketquest, Inc.

RM: George LaRocca, RM13
REVIEWER: Linda DeLuise

DECISION: 359290 [73510-2]
359637 [73510-5]

DP BARCODE: 319883 [73510-2]
321647 [73510-5]

ACTION: 570 [73510-2]
R34 [73510-5]

ACTIVE INGREDIENT(S): **73510-2**
109701, Permethrin.....45.0%
73510-5
105402, S-Methoprene.....1.2%
109701, Permethrin.....45.0%

TYPE: Flea and Tick Spot-On

OPPTS GUIDELINE(S): 810.1000
810.3000
810.3300

MRID: 46425801
46041303
45364808
46425801

GLP ?: No.

SITE(S): Dogs

PEST(S):

Fleas; Ticks; Mosquitoes

STUDY APPLICATION RATE:

Specific to dog weight class

LABEL APPLICATION RATE:

dogs < 15 lbs [EPA Reg. No. 73510-2]
dogs <33 lbs [EPA Reg. No. 73510-5]
dogs 15 to 33 lbs [EPA Reg. No. 73510-2]
dogs 33 to 66 lbs
dogs >66 lbs.

STUDY SUMMARY:

The registrant's representative provided a rebuttal letter to a previous Agency review and conditional letter of acceptance (12 July 2005).

The first point made was with regard to the acceptability of data submitted in support of tick claims. Data demonstrating efficacy against *Ixodes ricinus*, a species of tick known to transmit Lyme disease in Europe, were referenced instead of data generated against a native tick species (i.e., *Ix. scapularis* and/or *Ix. pacificus*). The basis of this argument was that (1) in considering a similar claim against ticks for EPA Reg. No. 773-73, the same data were found to support a claim (kills, repels, & prevents infestation) for up to 6 weeks against *Ix. scapularis* and (2) that the data provided should be considered to support claims against *Ixodes* spp. on the basis of likely physiological similarities within the taxon.

The second Agency determination rebutted dealt with the acceptability of data cited in support of claims against mosquitoes. The data referenced were used in support of mosquito claims for EPA Reg. No. 773-73. The representative stated that the same data were again cited in support of a 4 week mosquito claim for EPA Reg. No. 75257-1 "as recently as March 2005". This statement is incorrect. These data did not support the registration of EPA Reg. No. 75257-1. MDIR 46062801 (Weatherston, I. (2003) Product Performance: Treatments to Control Pests of Humans and Pets: Freedom 45 for Dogs. Project Number: 75257/R/2. Unpublished study prepared by Star Business Products, Inc. 66 p.) was reviewed by Kevin Sweeney in March 2004.

ENTOMOLOGIST'S COMMENTS AND RECOMMENDATIONS:

There is a discrepancy between the duration of effectiveness claimed and the re-application interval. If it is efficacious for up to 6 weeks, why is it a "monthly application" or "monthly flea and tick treatment"? Resolution of this issue is deferred to the product reviewer and product manager.

The rebuttals offered are addressed specifically below.

General Recommendations:**EPA Reg. Nos. 73510-2 and 73510-5**

1. Claims against ticks are acceptable on the basis of previously submitted data for *R. sanguineus* and *Ix. ricinus*. The registrant has provided reasonable arguments for the consideration of the data submitted.

- The claim "Deer Ticks (*Ixodes scapularis*) a vector of Lyme disease – up to 6 weeks" is acceptable.
 - Submit or cite data confirming the duration of effectiveness of the products against *Dermacentor variabilis* within 12 months for general tick claims.
2. Claims against mosquitoes are not acceptable on the basis of the data provided in MRID 46425801.
 - The registrant rebutted the conclusion of the previous review of *Aedes aegypti* data. It was asserted that the same data have been cited previously for similar claims other product labels (specifically EPA Reg. No. 75257-1). The registrant may wish to pursue an amendment via cite-all or selective citation.

Recommendations, specific to EPA Reg. No. 73510-2:

1. As per previous reviews of similar products (*i.e.*, 2 March 2004 and 1 September 2004), remove the "< 15 lb" and "15 – 33 lb" weight classes from the label. Replace with "< 33 lbs" weight class. State the application rate for dogs weighing less than 33 lbs as 1.5 mL.
2. Flea, Tick & Mosquito treatment.
 - **Conditionally Acceptable.** This claim was inadvertently accepted in the previous review. Include a time qualification for mosquitoes or remove them from the label, as "monthly application" and "monthly treatment" imply month long protections. Submit or cite confirmatory data within 12 months.

Recommendations, specific to EPA Reg. No. 73510-5:

1. Kills and Repels [adult] fleas for up to 5 weeks [per application]!
 - **Acceptable**
2. Kills, Repels and Prevents re-infestation of fleas for up to 5 weeks!
 - **Acceptable**
3. Kills and repels ticks for up to 6 weeks [per application]!
 - **Acceptable**
4. Kills and repels the Brown Dog Ticks (*Rhipicephalus sanguineus*) for up to 6 weeks [per application]!
 - **Acceptable**
5. Kills and repels ticks American Dog Ticks (*Dermacentor variabilis*) up to 3 to 4 weeks!
 - **Remove.** Submit or cite data in support of American Dog Ticks. As stated under the general recommendations, confirmatory data must be submitted within 12 months as a condition of general tick claims. At that time, the species specific claims may be re-evaluated at the request of the registrant.
6. Kills and repels fleas and ticks for up to 5 weeks [per application]!
 - **Acceptable**
7. Triple Protection against
 - Fleas
 - Ticks
 - Mosquitoes

- **Remove or Revise (Conditionally Acceptable).** The consumer is likely to understand this to mean that three active ingredients are present. Alternatively, remove the word "triple" resulting in the statement "Protection against: Fleas, Ticks, Mosquitoes." Include a time qualification for mosquitoes or remove them from the label, as "monthly application" and "monthly treatment" imply month long protection. Submit or cite confirmatory data within 12 months.
8. Flea, Tick & Mosquito treatment.
 - **Conditionally Acceptable.** Include a time qualification for mosquitoes or remove them from the label, as "monthly application" and "monthly treatment" imply month long protection. Submit or cite confirmatory data within 12 months.
 9. Kills mosquitoes that may vector heartworm.
 - **Remove.** Submit or cite data for a primary vector of canine heartworm (*i.e.*, *Aedes* sp. preferred)
 10. Kills, Repels, and Prevents reinfestation of ticks, including Brown Dog Ticks and *Ixodes* spp. which may be [are known to be] vectors of Lyme Disease, for up to 6 weeks.
 - **Remove** "[are known to be]".
 - **Modify** to read "for up to 5 weeks". Data for *Ixodes ricinus* support only a 5 week claim.
 11. Protects against blood feeding mosquitoes that may vector heartworm.
 - **Remove.** Submit or cite data for a primary vector of canine heartworm (*e.g.*, *Aedes* sp. preferred)
 12. Kills mosquitoes on dogs for up to 4 weeks.
 - **Remove.**
 13. MarketQuest One Drop Flea & Tick Control with OGR kills and repels ticks for up to 6 weeks, and kills mosquitoes on dogs.
 - **Modify** to read "for up to 5 weeks". Data for *Ixodes ricinus* support only a 5 week claim.

Review for 73510-2 (Dated 6 July 2005):

The following comments are relevant to the amendment submitted for EPA Reg. No. 73510-5.

Application Rate (mL)	Permethrin Applied (g)			
Dog Weight (lbs)	Studies (65%)	Label (45%)	Studies (65%)	Label (45%)
< 15	1.0	1.0	744 mg	515 mg
15 – 33	1.0	1.5	744 mg	772.5 mg
33 – 66	1.0	3.0	744 mg	1545 mg
> 66	2.0	6.0	1488 mg	3090 mg

Table 1. Amount of permethrin applied to dog weight classes for studies and according to subject product label directions.

Submitted Studies:

1. Endris, R.G. et al. 2002. Efficacy of Three Dose Volumes of Topically Applied 65% Permethrin Against *Ctenocephalides felis* and *Rhipicephalus sanguineus* on Dogs weighing 30 kg or More. *Veterinary Therapeutics*, 3(4):435-440.

The results of this study support only 4 week claims for both ticks and fleas. This may be an artifact of the size of dogs used. The difference between the application rate in this study and the label application rate make it difficult to ascertain the relevance of these data to the subject formulation.

2. Endris, R.G. et al. 2002. Efficacy of Two 65% Permethrin Spot-on Formulations Against Canine Infestations of *Ctenocephalides felis* and *Rhipicephalus sanguineus*. *Veterinary Therapeutics*, 3(3):326-333.

These results support the desired duration claims for fleas and ticks. This study supports 5 week flea and 6 week tick claims, at the label application rate. Greater than a 90% reduction in the number of fleas through day 35 and ticks through day 42 was observed.

3. Endris, R.G. et al. 2002. Repellency and Efficacy of 65% Permethrin and Selamectin Spot-on Formulations Against *Ixodes ricinus* Ticks on Dogs. *Veterinary Therapeutics*, 3(1):64-71.

The study compared the efficaciousness of a 65% permethrin product to a selamectin product against ticks. The tick *Ixodes ricinus* was used in this assay. Results were strong through 5 weeks. However, *Ixodes ricinus* is not a suitable test organism; tests should be performed on pest species indigenous to or established in the United States.

4. Endris, R.G. et al. 2000. Repellency and Efficacy of 65% Permethrin and 9.7% Fipronil Against *Ixodes ricinus*. *Veterinary Therapeutics*, 1(3):159-168.

The study compared the efficaciousness of a 65% permethrin product to a 9.7% fipronil product (Frontline®). The results were generally acceptable (>90% reduction through 14 days; >87% reduction through 28 days). However, as stated above, *Ixodes ricinus* is not a suitable test organism, tests should be performed on pest species indigenous to or established in the United States.

5. Meyer, J.A. et al. 2003. Repellency and Efficacy of 65% Permethrin Spot-on Formulation for Dogs Against *Aedes aegypti* (Diptera: Culicidae) Mosquitoes. *Veterinary Therapeutics*, 4(2):135-144.

The submission tested the effectiveness of a 65% permethrin spot-on against *Aedes aegypti* mosquitoes. The results of the experiment only weakly support any kill or repellency claims for mosquitoes. Mosquito landings were reduced by >90% only at 6 hours after treatment. The number of landings was statistically reduced, without consistency, only through 14 days. The results for mosquito mortality were slightly better, resulting in marginal mosquito mortality (>80%) for 3 weeks. The product did reduce feeding of mosquitoes through 28 days. The percent reduction in feeding ranged from 87.1 to 78.0 on days 1 through 21.

ENTOMOLOGIST'S COMMENTS AND RECOMMENDATION(S):

The data submitted generally support the repellency and kills claims for 5 week for fleas and 6 weeks for ticks. However, the 4 week mosquito claim and a claim against pasture ticks, which may transmit Lyme disease, are not supported. Based upon the data submitted, mosquitoes may be added to the label, but no duration of protection greater than 6 hours may be included. Data may be submitted or cited to satisfy the requirements for a 4 week claim in the future. Pasture ticks (which may transmit Lyme disease) may not be added to the label, as these arthropods are not typically found in the U.S.

Enclosure

073510-00002-00005 S782804-ER

PRODUCT PERFORMANCE/EFFICACY REVIEW

BY

Kevin J. Sweeney, Entomologist, IB

Kevin J. Sweeney
3/2/04

Date: March 2, 2004

Reviewer: George LaRocca

PM: PM 13, George LaRocca

Product Reg. No: 73510 -2 and 73510-L

Product Names: Marketquest One Drop Flea & Tick Control
Marketquest One Drop Flea and Tick Control with IGR

Decision # 331704 and 331701

DP: 293541 and 295707

OPPTS Guideline: 810.3300

Chemical: permethrin 45% (-2 product)
Permethrin 45% and S-methoprene 1.2% (-L product)

Use pattern: RTU spot-on for dogs

Accepted Application rate: -2 product (3/1/02 accepted label)
Apply 1.5 ml per dog (**33 lbs. or less**) every 4 weeks.
Apply 3.0 ml for dogs (33 lbs or more) every 4 weeks.
No directions for larger dogs

Proposed application rates -2 amendment and - L product
Apply 1.0 ml per dog (15 lbs. or less) every 4 weeks.
Apply 1.5 ml per dog (15 to 33 lbs.) every 4 weeks.
Apply 3.0 ml per dog (33 to 66 lbs.) every 4 weeks.
Apply 4.5 ml per dog (> 66 lbs.) every 4 weeks.

Accepted Pests: kill/repel fleas and ticks

Proposed pests:

-2 and -L

Kills/repels fleas and ticks.

Kills mosquitoes.

Protects against mosquitoes (vectors of heartworm). Also kills and repels deer ticks and

brown dog ticks.

-L only stops flea eggs from hatching

Submitted Studies and Method of Support:

The method of support for product performance appears to be the selective method (or cite all option) and the following product performance studies were submitted.

MRID 46039501 Efficacy evaluation of a permethrin squeeze-on against adult cat fleas, adult brown dog ticks, nymphal deer ticks, and *Aedes aegypti* mosquitoes.

The submitted data tested the reduced application rate for small dogs under 15 lbs and large dogs over 66 lbs. when compared to previously accepted permethrin studies for spot-on labels. The data were quite variable between test groups and between post-treatment test days. A consistent product performance trend was not always evident. In addition, 6 animals were used for the dogs in the lower weight ranges but only three in the upper weight ranges. The small sample size probably contributed to the variability of the results.

MRID 46041303 Dose Titration of an s-methoprene Spot-on Dogs. Final Report, Statistical Analyses and Conclusions.

The study used only 2 dogs per treatment and did not test the range of animal weights listed on the product label. This is not even close to a OPPTS 810.3300 guideline study. The study seems like confirmatory data but no additional studies are cited for methoprene in the data matrix other than this one.

Entomologist Recommendation and Comments:

1. Based on the data submitted, the use of less than 1.5 ml of product on dogs 15 lbs. or less is not acceptable. The reduction of volume for larger animals was not acceptable either. The data were too inconsistent. Also, small dogs were not tested with s-methoprene at the proposed volume.

2. In addition, the currently accepted label for 73510-2 should add separate directions for large dogs as was the case for the original labels submitted in 2001. In Vern McFarland's review from June 2001, he noted that 6.0 ml should be applied to large dogs weighing more than 66 lbs. Four weight ranges were listed and Mr. McFarland reviewed labels and accepted them. The customary treatments remained on pending labels through November 16, 2001 but in February 2002, the labels were changed and ultimately were approved in March 2002 using only two dog weight ranges. This resulted in a product applying less permethrin to a dog than the other products in the industry without submitted or cited product performance data. The data submitted with the current amendment do not support the lower dose labeling claims.

3. The mosquitoes claims are unacceptable for both products. The % kill was too low and many mosquitoes were feeding, therefore, the product did not repel mosquitoes or protect the dog from mosquito bites, disease vectors, or diseases. For instance, in the control, the mean on Day 8 was 18 blood fed mosquitoes while one treatment had 11 blood fed mosquitoes and the other 6.

4. Generally, the efficacy of the product should be evaluated at the 24 hour post-treatment interval, not at 48 or 72 hours. Evaluation of longer exposure times can be helpful sometimes but the spot-on should have repelled or killed the arthropod at 24 hours. In the submitted studies, the product failed after 16 days for small dogs under 15 lbs. (see table 12) for both flea and tick control and failed by three weeks for all treatment groups. The data only support an "up to 3 week" claim for all dog groups except those below 15 lbs. These data were not supportive of four weeks control. The registrant appears to have made an offer to pay to retain the 4 week control claim but it is unclear if this included product performance data (supported by the selective method?) because they submitted studies and listed them on the data matrix.

5. The claim for *Ixodes scapularis*, the deer tick or blacklegged tick, is not acceptable.